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EXAMINER	
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ART UNIT	PAPER NUMBER
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/757,054	PETITTE ET AL.	
	Examiner	Art Unit	
	Michael C. Wilson	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 February 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *44,47,48 and 51-57* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *44,47,48 and 51-57* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *2-7-5*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 2-7-05 has been entered.

Applicant's arguments filed 2-7-05 have been fully considered but they are not persuasive.

Claims 1-43, 45, 46, 49, 50 have been cancelled. Claims 56 and 57 have been added. Claims 44, 47, 48 and 51-57 are pending and under consideration in the instant office action.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC ' 112

New Matter

Claims 53 and 54 remain rejected and claims 44, 47, 48, 51, 52, 56 and 57 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled

in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for reasons of record.

Claims 53 and 54 remain new matter because the specification did not contemplate maintaining the ES cell phenotype for one or two months. Applicants point to pg 13, line 21, through pg 14, line 7 (pg 14-15 of response). Applicants' argument is not persuasive. The citation teaches:

> "In a preferred embodiment, avian embryonic gonadal cells comprising primordial germ cells from a four to five day incubated avian embryo are seeded onto the preconditioned feeder matrix with conditioned media, and the avian cells give rise to nests or colonies of cells exhibiting an embryonic stem cell pheno [sic]Unlike the case with mammalian cells, it is currently preferred to have a preconditioned feeder matrix to facilitate the survival and development of avian PGCS into undifferentiated avian cells expressing an ESC phenotype. The avian embryo cells of the present invention can be cultured for at least one or two months as is typical for a primary cell culture, which is significantly greater than the usual two week life of primary cultures of cells from an unincubated avian embryo." (underlining added)

The sentence that mentions culturing for one or two months in context is limited to the avian embryo cells in culture. While the cells may be capable of producing cells with an ES cell phenotype, nowhere does the citation imply that the ES cell phenotype is maintained for one or two months. It is not readily apparent that the "avian cells of the present invention" that "can be cultured for at least one or two months" maintain the ES cell phenotype for one or two months.

Applicants argue that the sentences prior to mentioning the avian cells of the invention can be cultured for at least one or two months mention cells exhibiting an ES cell phenotype. Therefore, applicants conclude it is readily apparent that the cells cultured for at least one or two months have the ES cell phenotype for one or two

months. Applicants' arguments are not persuasive. No such conclusion can be made based on the paragraph bridging pg 13-14. The paragraph discusses culturing PGCs to obtain colonies of cells having an ES cell phenotype, then states the cells of the invention can be cultured for at least one or two months. As written, one of skill would only conclude that the PGCs in which colonies of cells having an ES cell phenotype appear are cultured for one to two months. One of skill in the art would not conclude that maintaining cells for at least one or two months applied to the smaller genus of cells having an ES cell phenotype.

The phase "one or more colonies" in claim 44 is new matter. The specification discusses obtaining colonies but does not contemplate the lower limit of "one" colony as now claimed. The support provided by applicants in the response filed 2-7-05 is limited to producing colonies.

Enablement

Claims 44, 47, 48, 51-55 remain rejected and claims 56 and 57 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a culture comprising chicken ES cells does not reasonably provide enablement for i) a culture of avian ES cells other than chicken ES cells or ii) a culture wherein ES cells are maintained for one or two months. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims for reasons of record.

Claim 44 is drawn to a sustained culture of undifferentiated avian cells expressing an embryonic stem cell phenotype, comprising a preconditioned feeder matrix, conditioned media, and avian primordial germ cells and avian stromal cells, wherein the avian primordial germ cells and stromal cells are isolated together from the embryonic genital ridge or gonad from an avian embryo at a stage later than stage 14 according to the Hamburger & Hamilton staging system and grown in the sustained culture to produce one or more colonies of undifferentiated avian cells expressing an embryonic stem cell phenotype. The sustained culture can be from any species of avian.

For enablement purposes, an avian cell expressing an ES cell phenotype as claimed is limited to an avian ES cell capable of becoming both a somatic and germ cell upon being introduced into an embryo. Pain (1996, Development, Vol. 122, pg 2339-2348) described avian ES as being capable of participating in the development of all cell lineages including the germline upon being implanted into a recipient blastocyst (pg 2339, col. 1, line 12). Applicants' previous disclosure acknowledged that ES cells formed somatic and germ cells upon being introduced into a recipient embryo (Petitte US Patent 5,656,479, Aug. 12, 1997, col. 1, lines 25-27). Thus, the art at the time of filing taught ES cells were defined as being capable of forming somatic and germs upon being injected into a blastocyst. The specification states, "embryonic stem cell phenotype refers to undifferentiated avian cells having a large nucleus, prominent nucleolus and little cytoplasm" (pg 9, lines 4-5). However, it is not readily apparent that pg 9, line 4-5, is intended to redefine ES cells as any undifferentiated avian cells having

a large nucleus, prominent nucleolus and little cytoplasm because it may be merely describing characteristics of ES cells known in the art as in applicants previous disclosure ('479). The specification does not provide any use for cells having an ES cell phenotype other than to make transgenic avians. Because the metes and bounds of cells having an ES cell phenotype are so unclear (see 112/2nd) and because the sole disclosed purpose for such cells is to make transgenic avians, cells expressing an ES cell phenotype as claimed must be able to become both a somatic and germ cell upon being introduced into an embryo, which is the phenotype used in the art at the time of filing that defines ES cells.

Reference by the examiner in the enablement rejection to an avian or chicken ES cell is limited to an avian or chicken cell capable of becoming both a somatic and germ cell upon being introduced into an embryo.

Claims 44, 47, 48, 51-57 are not enabled for any species of avian ES cell other than chicken. Bakst (1997, Poultry Sci., Vol. 76, pg 83-90) taught the Eyal-Giladi and Kochav procedure (1976, (dependent upon the Hamilton & Hamilton procedure, 1951, claimed) procedure for staging chickens was not applicable to turkeys (¶ bridging pg 83-84). Thus, the staging of chicken embryos did not necessarily apply to avians of other species. Pain (Cells Tissues Organs, 1999, Vol. 165, pg 212-219) taught mammalian germline transmission had only been obtained in mice despite attempts to do so in other mammalian species. The only other species that had shown germline transmission was chickens (pg 212, col. 2). The art did not teach ES cells in any avian species other than chickens. The specification does not correlate the ES cells obtained in chickens with

any other avian species and is silent regarding the differences between the stages of chickens and other avians. The specification does not disclose how to overcome the failure to correlate mouse ES cells to other mammalian species known in the art so one of skill would expect chicken ES cells to correlate to other avian species. Without proper staging information, without evidence of ES cells in avian species other than chickens and without any correlation between chickens and other avian species in the specification, it would have required one of skill undue experimentation to determine how to isolate avian ES cells in avian species other than chickens. Limiting the claims to chicken cells would overcome this rejection.

Applicants argue the specification enables culturing any avian cell as broadly claimed (pg 11). Applicants point out that the specification describes the appropriate stage as after stage 14, or after formation of the primitive streak. Applicants' argument is not persuasive. While the cells may be cultured and may have characteristics of ES cells, applicants have not provided adequate guidance or correlation indicating the cells from other species would be capable of providing germline and somatic cell transmission upon being introduced into a recipient embryo.

Claims 53 and 54 remain rejected because the specification does not enable maintaining chicken ES cells (or any other avian ES cells) for at least one or two months as claimed. Claims 53 and 54 are drawn to the sustained culture of claim 44, wherein the ES cell phenotype is maintained for at least one or two months. Simkiss (1990, 4th World Congr. Genetic Appl. Livestock Prod., Vol. 16, pg 111-114) and Petitte (1990, Development, Vol. 108, pg 185-195), both of record, taught chicken PGCs capable of

producing somatic and germ cell chimeric chickens. Ponce De Leon of record (1997, Revista Brasileira de Reproducao Animal, Vol. 21, pg 96-101) taught LIF, bFGF, IGF and SCF are required for long-term culture of chicken PGCs (pg 100, col. 2, about half way down). In context, the PGCs of Ponce de Leon are ES cells because they provide germ and somatic cell chimeras upon being introduced into recipient embryos (pg 100, "Results and Discussion," lines 1-7). The art did not teach how to culture avian PGCs having an ES cell phenotype for one or two months.

The specification taught culturing avian PGCs on "preconditioned" STO feeder cells (Examples 1-3). The specification suggests the "avian embryo cells of the present invention can be cultured for at least one or two months as is typical for a primary cell culture" (pg 14, lines 4-5). The citation on pg 14, line 4-5, does not describe how to maintain the ES cell phenotype for one to two months as claimed. The specification does not teach the amounts of essential growth factors required to culture avian ES cells in the presence of feeder cells for one or two months. The specification does not exemplify maintaining the ES cell phenotype for at least one or two months. Given the teachings in the art which describe the specific conditions of LIF, bFGF, IGF and SCF as being essential to culture ES cells long term (Ponce de Leon) taken with the state of the art, i.e. that avian ES cells had not been cultured for one or two months as claimed, and the lack of guidance provided in the specification, it would have required one of skill undue experimentation to overcome the state of the art and determine which of the multitude of LIF, bFGF, IGF and SCF concentrations maintained chicken ES cells for at least one or two months as claimed. In fact, it would have required one of skill undue

experimentation to overcome the state of the art because media comprising LIF, bFGF, IGF and SCF may lack essential ingredients to maintain ES cells for at least one or two months, i.e. media comprising LIF, bFGF, IGF and SCF may not be capable of maintaining chicken ES cells for at least one or two months. Deleting claims 53 and 54 would overcome this rejection.

Applicants argue Ponce de Leon does not disclose the conditions of LIF, bFGF, IGF and SCF that did provide long term culture of PGCs. Therefore, applicants conclude it is not possible to determine what LIF, bFGF, IGF and SCF conditions were necessary to sustain culture for one or two months. Applicants' argument is not persuasive and actually strengthens the examiners position. Applicants essentially admit that based on the teachings of Ponce de Leon, one of skill could not determine what LIF, bFGF, IGF and SCF conditions were necessary to sustain culture for one or two months. Ponce de Leon describes PGC culture conditions and concludes LIF, bFGF, IGF and SCF were essential for long-term culture; Ponce de Leon need not reveal the LIF, bFGF, IGF and SCF conditions used to come to such a conclusion. The specification does not teach the LIF, bFGF, IGF and SCF conditions that are essential to maintain ES cells for one or two months as claimed. Therefore, the burden would have been undue to experiment with LIF, bFGF, IGF and SCF conditions to obtain that which had not been obtained in the art because of the multitude of conditions required to test and because the combination LIF, bFGF, IGF and SCF may lack essential elements required to maintain ES cells for at least one or two months.

Applicants' arguments in the paragraph bridging pg 10-11 of the response are off point. Applicants' imply the examiner has questioned why applicants' invention works. The examiner has not made any such allegation. The examiner has questioned whether applicants have provided adequate guidance for one of skill to culture avian ES cells for one or two months given the state of the art taken with the lack of guidance in the specification and the amount of experimentation required to obtain that which had not yet been obtained.

In view of the dearth of information in the art at the time of filing required for one of skill to isolate any avian ES cell other than chicken ES cells or to maintain chicken ES cell for one or two months as claimed, the parameters required to obtain such a result are essential to the invention. Because the specification does not teach the essential elements required to obtain results not known in the art, the amount of experimentation required by one of skill to obtain such results is, by its very nature, undue. Examples 1, 2 and 3 merely reiterate parameters known in the art. Pg 4, line 18-20, pg 8, lines 20-22 and pg 12, lines 4-8, merely list avian species. The teachings cited do not overcome the unpredictability in the art by providing the specific conditions required to isolate any avian ES cell other than chicken ES cells or to maintain any ES cell for one or two months as broadly claimed. The conditions described in the specification are not "a reasonable amount of guidance" because they are not distinguishable from conditions known in the art. The conditions described in the specification are not adequate for one of skill to determine the parameters required to obtain results not known in the art. Therefore, it would have required one of skill undue experimentation to isolate any avian

ES cell other than chicken ES cells or to maintain chicken ES cell for one or two months as claimed.

Indefiniteness

Claims 44, 47, 48 and 51-55 remain rejected and claims 56 and 57 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for reasons of record.

The cells encompassed by the phrase "undifferentiated avian cells expressing an embryonic stem cell phenotype" are unclear (claim 44). It is unclear if the cells merely share a phenotype in common with avian ES cells or if the cells are avian ES cells capable of making germline chimeras upon being introduced into a recipient embryo. The specification states, "embryonic stem cell phenotype refers to undifferentiated avian cells having a large nucleus, prominent nucleolus and little cytoplasm" (pg 9, lines 4-5). Such a description is ambiguous because it cannot be determined what applicants consider "large," "prominent" or "little." The description is also ambiguous because a phenotype cannot be defined as cells. The phrase "refers to" on pg 9, line 4, makes the citation even more unclear because it cannot be determined if "refers to" is intended to define the phenotype or merely to describing to what the phenotype is relevant. Therefore, it is unclear if "undifferentiated avian cells having a large nucleus, a prominent nucleolus, and little cytoplasm" is the "embryonic stem cell phenotype" or a description of a feature of an "embryonic stem cell phenotype." Ergo, it is unclear if

"avian cells expressing an ES cell phenotype" are defined as any "undifferentiated avian cells having a large nucleus, a prominent nucleolus, and little cytoplasm" or if "avian cells expressing an ES cell phenotype" have to do with (are relevant to) "undifferentiated avian cells having a large nucleus, a prominent nucleolus, and little cytoplasm." The specification also states an "'undifferentiated avian cell expressing an embryonic stem cell phenotype' encompasses cells derived from avian primordial germ cells and is therefore used to describe the cells cultured in accordance with the process of the present invention" (pg 9, lines 19-22). It is unclear if pg 9, lines 19-22, is the definition of "avian cells expressing an ES cell phenotype." The scope of cells encompassed by the description on pg 9, lines 4-5, is different than the scope of the cells encompassed by the description on pg 9, lines 19-22. One of skill would not be able to determine whether to use pg 9, lines 4-5, or pg 9, lines 19-22, as the definition of "avian cells expressing an ES cell phenotype" as claimed. In fact, one of skill would not have been able to determine that either citation was a definition of "avian cells expressing an ES cell phenotype" and not merely a description of features shared by "avian cells expressing an ES cell phenotype." Furthermore cells do not "express" a phenotype as on pg 9, line 19. Pg 1, line 17, states ES cell were capable of making germline chimeras. The phrase "embryonic stem cell phenotype" is mentioned on pg 3, lines 4-5, but does not clarify the meaning. One of skill in the art at the time of filing would have been unclear as to whether the specification was redefining ES cells or refining the art recognized meaning of ES cells as embryonic stem cells capable of

making germline chimeras upon being introduced into a recipient embryo. Therefore, the metes and bounds of cells encompassed by the phrase cannot be determined.

Applicants argue the term is defined in the specification. Applicants' argument is not persuasive. The "definition" is too unclear to determine the metes and bounds of the term ("embryonic stem cell phenotype refers to undifferentiated avian cells having a large nucleus, prominent nucleolus and little cytoplasm" (pg 9, lines 4-5). One of skill would not conclude from pg 9, lines 4-5, that applicants were attempting to redefine ES cells as undifferentiated cells having a large nucleus, prominent nucleolus and little cytoplasm because the definition is so completely different than the art recognized definition of ES cells phrase may be describing features of ES cells known in the art. One of skill could not determine which undifferentiated avian cells were encompassed by the term because the specification does not define what applicants consider a large nucleus, prominent nucleolus and little cytoplasm.

Applicants argue those of skill would recognize the term as cells with a certain morphology that those of skill in the ES cell art recognize as being "characteristic of ES cells and ES-like cells: namely, a large nucleus, a prominent nucleolus, and little cytoplasm." Applicants' arguments are not persuasive. One of skill would not reasonably conclude that the term encompasses "ES-like cells." One of skill would not be able to determine how much the undifferentiated cells must be "like" cells capable of germ and somatic cell transmission upon being introduced into a recipient embryo or how large, prominent or little the nucleus, nucleolus and cytoplasm must be to be considered "ES-like" cells.

It remains unclear how PGCs isolated from an embryo later than stage 14 are distinguished from PGCs isolated from a stage X or stage 14 embryo (claim 44, 47, 48). PGCs isolated from stage X, 14 and after stage 14 embryos have the same structure and function as supported by Ponce de Leon, of record, who used PGCs from Stage 13-14 embryos (pg 99, col. 1, about halfway down), Petitte, of record, who used PGCs from Stage X embryos (abstract) and Naito, of record, who used PGCs from Stage 13-15 embryos (pg 322, col. 1, "Preparation of PGCs for preservation"). Each of the PGCs were capable of germline transmission upon being transplanted into a recipient embryo. As such, the structural/functional distinction of PGCs isolated after stage XIV as claimed cannot be determined. Applicants have provided no new arguments regarding this rejection.

For art purposes, the process limitation of isolating cells from a genital ridge or gonad after a stage greater than stage 14 in claim 44 does not bear patentable weight on the product claimed because it is a process step that does not alter the structure or function of the cells isolated. Avian cells having an ES phenotype as claimed can be isolated by means other than from a germinal ridge or gonad after stage 14 as claimed. Avian cells having an ES cell phenotype isolated from the genital ridge or gonad of an embryo after stage 14 as claimed do not have any distinguishing structure or function as compared to other avian cells having an ES cell phenotype known in the art. In addition, the limitation of isolating PGCs with stromal cells does not bear patentable weight because isolating the PGCs and stromal cells separately and mixing them

together can obtain the product. Isolating the avian cells having an ES cell phenotype with the stromal cells would not alter the structure and function of the cells as compared to isolating the cells separately.

Claim Rejections - 35 USC ' 102

Claims 44, 47, 48, 52-55 remain rejected under 35 U.S.C. 102(b) as being anticipated by Chang (1995, Cell Biol. Internatl. Vol. 19. No. 2, pg 143-149) for reasons of record.

Chang taught making feeder cells by isolating cells from the genital ridge of day 5 embryos and culturing the cells for 4 or 5 days (pg 143, "Preparation of germinal ridge and culture of stroma cells"; pg 146, description of Fig. 2; pg 147, Fig. 2). The feeder cells are "preconditioned" because they are in culture for 4 days prior to the addition of day-2 PGCs. The feeder cell media is "conditioned" because it contains biologically active components obtained from the previous 4 days in culture prior to adding day-2 PGCs. The cells isolated from the genital ridge of day 5 embryos comprised stromal cells (pg 144, line 6) and PGCs because Chang described the day 5 PGCs in Fig. 2 (pg 146). In addition, isolating cells from the genital ridge as described by Chang inherently results in isolating stromal cells and PGCs at the same time as claimed because the specification specifically contemplates isolating cells from the gonad of a day 5 embryo on pg 13, line 22. Day 5 embryos are greater than stage 14 as claimed because day 2 embryos are stage 14 (pg 144, col. 2, lines 1-10). The conditioned media taught by Chang had LIF, IGF and FGF-b (pg 144, col. 1, 1st full ¶). Claims 53 and 54 are

included because cells isolated from the genital ridge of a day 5 embryo and cultured as described by Chang do not differ from cells isolated from a similar culture, wherein the ES cell phenotype is maintained for one or two months as claimed. The structure and function of a culture of cells in which the ES cell phenotype is maintained for 4 days is equivalent to a culture in which the ES cell phenotype is maintained for one or two months. Culturing the cells for one or two months does not alter the structure or function of the culture. The limitations in claims 53 and 54 do not distinguish the structure or function of the cells within the culture or the components of the culture from those known in the art. The PGCs that grew for 4-5 days in culture (Fig. 2, pg 146-147) are colonies of cells as claimed because they are in different wells of a tissue culture plate.

Applicants argue Chang did not teach the PGCs and stromal cells were isolated together. Applicants' argument is not persuasive. The cells isolated from the genital ridge of day 5 embryos comprised stromal cells (pg 144, line 6) and PGCs because Chang described the PGCs isolated from day 5 embryos were cultured for 5 days (Fig. 2, pg 146 and 147). In addition, isolating cells from the genital ridge as described by Chang inherently results in isolating stromal cells and PGCs at the same time as claimed because the specification specifically contemplates isolating cells from the gonad of a day 5 embryo on pg 13, line 22.

Applicants argue Chang did not teach obtaining a change in either the phenotype or behavior of the isolated cells. Applicants' argument is not persuasive. The claims do not require a change in the phenotype or behavior of the isolated cells. Furthermore,

the cells isolated by Chang have the same structure as those contemplated in the specification on pg 13, line 22, as being part of the invention.

While Chang added cells from the heart or vitelline vein of 2 day old chick embryos to the cells isolated from day 5 embryos, Chang clearly teaches that both stromal cells and PGCs were isolated from the genital ridge of day 5 embryos (pg 144, line 6, and pg 146 and 147, Fig. 2).

Applicants argue the PGCs of Chang were terminally differentiated. Therefore, applicants conclude the PGCs of Chang are not undifferentiated cells as claimed. Applicants' argument is not persuasive. The claims encompass cultures comprising avian cells having any ES cell phenotype. The PGCs of Chang meet the limitation because they are obtained during development and contribute to the gonads – a phenotype of ES cells.

Claims 44, 47, 48 and 52-55 remain rejected under 35 U.S.C. 102(b) as being anticipated by Chang (1997, Cell Biol. Internatl., Vol. 21, No. 8, pg 495-499) for reasons of record.

Chang taught isolating genital ridge stromal cells from day 5 (stage 27-28) embryos. The cells were cultured for 5 days in media containing IGF, FGF and LIF with germinal ridge stromal feeder cells isolated from day 5 embryos. gPGCs obtained from the culture were injected into recipient embryos and provided germline transmission (pg 496, "Preparation and culture of gPGCs"; pg 497, Fig. 1, "Progeny of germline chimeric

chickens"). The gPGCs that grew well in the 5-day culture (pg 496, col. 2, line 8) are colonies as claimed because they are together in different wells of a tissue culture plate.

The "primary cultured GRSCs" (last sentence of "Preparation and culture of gPGCs") are a "preconditioned feeder matrix" because they were in culture prior to the addition of other GRSCs. The media of the "primary cultured GRSCs" was "conditioned" because it contained biologically active components obtained from the previous days in culture prior to adding other GRSCs. The cells isolated from the genital ridge and added to the "primary cultured GRSC" feeder cells inherently comprised stromal cells and PGCs. Day 5 embryos are stage 27 (pg 496, "Preparation and culture of gPGCs", line 2). Claim 51 has been withdrawn from the rejection because Chang did not teach using BRL conditioned media. The conditioned media taught by Chang had LIF, IGF and FGF-b (pg 496, "Preparation and culture of gPGCs"). A PGC culture maintained for one or two months as claimed (claims 53, 54) does not differ from PGC cultures known in the art because their structure and functions are equivalent and because culturing PGCs for one or two months does not alter the structure or function of the culture. Therefore, the limitations in claims 53 and 54 do not bear patentable weight in considering the art because they does not distinguish the structure or function of the cells within the culture or the components of the culture from those known in the art.

Applicants argue Chang did not teach a culture comprising one or more colonies of undifferentiated avian cells. Applicants argue one of skill would recognize that gentle pipetting would without the use of digestive enzymes would fail to release colonies of

undifferentiated cells. Applicant's argument is not persuasive. The claims do not require releasing colonies of undifferentiated cells or clumps of cells. The gPGCs that grew well in the 5-day culture (pg 496, col. 2, line 8) are colonies of cells as claimed because they are in different wells of a tissue culture plate.

Applicants argue the cells described by Chang are merely PGCs. Applicants' argument is not persuasive. The PGCs described by Chang became both a somatic and germ cell upon being introduced into an embryo (pg 496, "Preparation and culture of gPGCs"; pg 497, Fig. 1, "Progeny of germline chimeric chickens").

Claims 44, 47, 48 and 51-55 remain and claims 56 and 57 are rejected under 35 U.S.C. 102(e) as being anticipated by Petitte (US Patent 5,340,740), Petitte (US Patent 5,656,479) or Petitte (US Patent 5,830,510) for reasons of record.

Petitte taught isolating and dissociating whole stage X chicken embryos, seeding the cells onto a preconditioned mouse STO feeder layer, culturing the cells with BRL conditioned medium and obtaining PGCs (col. 7, lines 7-14, of '740; col. 6, line 44, of '479; col. 6, line 54-65, of '510). The PGCs and stromal cells were inherently "isolated together from the embryonic genital ridge or gonad" as claimed because the whole embryo was isolated and inherently contained both PGCs and stromal cells in the genital ridge or gonad. The PGCs and stromal cells in the whole dissociated embryo taught by Petitte are equivalent to PGCs and stromal cells isolated from the embryonic genital ridge or gonad as claimed because they have the same structure and function. PGCs and stromal cells from the stage X taught by Petitte are equivalent to PGCs and

stromal cells isolated from an embryo later than stage 14 as claimed because they have the same structure and function.

Applicants assert that PGCs isolated later than stage 14 are committed to terminal differentiation and are not the same as PGCs isolated from stage X embryos. Applicants argue the cells of Petitte are not isolated from an embryo later than stage 14. Therefore, applicants conclude Petitte does not teach every element of the claims. Applicants' argument is not persuasive. Applicants' assertion that PGCs isolated later than stage 14 are committed to terminal differentiation is unfounded. Since the patent office does not have the ability to determine the similarities between stage X and stage 15 PGCs, applicants must provide evidence that PGCs isolated after stage 14 as claimed cannot have the same structure as PGCs isolated from stage X embryos as described by Petitte. Applicants' argument is also confusing because the cells in the claims can have any ES cell phenotype. therefore, without evidence to the contrary, the cells of Petitte share a common structure and function as PGCs isolated from embryos at a stage greater than 14 as claimed. Cells having an ES cell phenotype isolated from stage X as described by Petitte are equivalent to cells isolated from a stage greater than 14 and having an ES cell phenotype as broadly claimed.

Applicants argue Stage X embryos do not have a genital ridge or gonad. Therefore, applicants conclude the cells isolated from whole Stage X embryos described by Petitte are not the same as cells isolated from the genital ridge or gonad of an embryo at a stage greater than Stage 14 having an ES cell phenotype. Applicants' argument is not persuasive. The PGCs of Petitte are capable of becoming somatic or

germ cells, which is an ES cell phenotype as claimed. The process limitation of isolating cells from a genital ridge or gonad after a stage greater than stage 14 as claimed does not bear patentable weight on the product claimed because the product (stromal cells and cells having an ES cell phenotype) can be isolated from either a whole stage X embryo or the genital ridge of a stage 15 embryo.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 44, 47, 48 and 51-57 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ponce de Leon (US Patent 6,156,569) in view of Chang (1995, Cell Biol. Internat'l, Vol. 19, page 143-9).

Ponce de Leon isolated PGCs from the dorsal aorta of stage XIV avian embryos. The cells were cultured with complete medium, LIF, FGF, IGF and SCF for at least 25 days (col. 7, line 43 through col. 8, line 53). PGCs isolated from the dorsal aorta of a stage XIV embryo as described by Ponce de Leon are equivalent to PGCs isolated from the germinal ridge of an avian embryo after stage 14 as claimed because the PGCs were capable of creating a chimeric chicken - a phenotype of ES cells. The limitation of collecting PGCs from an avian embryo later than stage 14 or together with avian stromal cells as claimed does not bear patentable weight on the product claimed

because it is a process step that does not distinguish the structure or function of the PGCs from those taught by Ponce de Leon. The limitation of isolating PGCs at the same time as stromal cells does not bear patentable weight on the product claimed because it is a process step that does not alter the structure of function of the PGCs from those taught by Ponce de Leon. Ponce de Leon did not teach culturing the PGCs with avian stromal cells isolated from the germinal ridge of an avian embryo after Stage 14.

However, Chang taught culturing PGCs with avian stromal cells isolated from the germinal ridge of an avian embryo at a stage later than stage 14. Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to culture PGCs as described by Ponce de Leon with stromal cells isolated from the germinal ridge of an avian embryo at a stage later than stage 14 as described by Chang. One of ordinary skill in the art at the time the invention was made would have been motivated to culture PGCs described by Ponce de Leon with avian stromal cells isolated from the germinal ridge of an avian embryo at a stage later than stage 14 as described by Chang to increase the number of PGCs as taught by Chang (abstract).

Thus, Applicants' claimed invention as a whole is *prima facie* obvious in the absence of evidence to the contrary.

Double Patenting

The process limitation of isolating cells from a genital ridge or gonad after a stage greater than stage 14 in claim 44 does not bear patentable weight on the product

claimed because the product (stromal cells and cells having an ES cell phenotype) can be isolated from either a whole stage X embryo or the genital ridge of a stage 15 embryo. In addition, the limitation does not bear patentable weight because the product claimed can be obtained by isolating the PGCs and stromal cells separately, i.e. isolating PGCs from a Stage X embryo and isolating avian stromal cells from the germinal ridge of a Stage 15 embryo. The culture obtained by combining PGCs from a Stage X embryo and stromal cells isolated from the germinal ridge of a Stage 15 embryo would have the same structure and function as the culture claimed.

Claims 44, 47, 48 and 51-55 remain rejected and claims 56 and 57 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1 and 8-10 of U.S. Patent No. 5,340,740 in view of the disclosure of '740 and Chang (1995, Cell Biol. Internat'l, Vol. 19, page 143-9).

Claims 1 and 8-10 of '740 are directed toward a sustained culture of undifferentiated avian cells having an ES cell phenotype maintained on a mouse fibroblast feeder layer. The cells were isolated from the area pellucida of Stage X embryos and cultured on mouse STO cells (Example 5). The cells isolated from Stage X embryos described and claimed in '740 are equivalent to the undifferentiated cells isolated from an avian embryo after stage 14 as claimed because they both have an ES cell phenotype. The cells isolated in Example 5 inherently comprise stromal cells, which is equivalent to avian feeder cells as claimed in the instant invention. Thus, the claims of '740 in view of the disclosure of '740 meet all the limitations of claim 44 in the instant

invention. The subject matter claimed in the instant application was fully disclosed in the patent and was covered by the patent since the patent and the application are claiming common subject matter. There is no apparent reason why applicant was prevented from presenting claims directed toward a culture comprising PGCs and avian stromal cells isolated together from stage IX-XIV embryos during prosecution of the application, which matured into a patent. See *In re Schneller*, 397 F.2d 350, 158 USPQ 210 (CCPA 1968). See also MPEP § 804.

In the alternative, '740 did not specifically teach a culture comprising PGCs and avian stromal cells isolated from the germinal ridge of an avian embryo at a stage later than stage 14.

However, at the time of filing, Chang taught culturing PGCs with avian stromal cells isolated from the germinal ridge of an avian embryo at a stage later than stage 14. Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to culture PGCs as described by Petitte with avian stromal cells isolated from the germinal ridge of an avian embryo at a stage later than stage 14 as described by Chang. One of ordinary skill in the art at the time the invention was made would have been motivated to use avian stromal cells isolated from the germinal ridge of an avian embryo at a stage later than stage 14 as described by Chang to increase the number of PGCs as taught by Chang (abstract).

Applicants are Chang did not teach the production of colonies. Applicants' argument is not persuasive. The method of '740 meets the limitation of producing at least one or more colonies of cells having an ES cell phenotype as claimed. In addition,

the PGCs that grew for 4-5 days in culture taught by Chang (Fig. 2, pg 146-147) are colonies of cells as claimed because they are in different wells of a tissue culture plate.

Applicants argue the motivational statement is invalid because one of ordinary skill in the art would not expect PGCs isolated after stage 14 to be capable of forming the claimed culture. Applicants' argument is not persuasive. The claim is drawn to a cell culture and is not drawn to a method of isolating PGCs after stage 14. The process limitation of isolating cells from a genital ridge or gonad after a stage greater than stage 14 as claimed does not bear patentable weight on the product claimed because the product (stromal cells and cells having an ES cell phenotype) can be isolated from either a whole stage X embryo or the genital ridge of a stage 15 embryo or by mixing PGCs isolated from Stage X embryos with stromal cells isolated from the germinal ridge of Stage XV embryos.

Applicants argue the PGCs of Chang were terminally differentiated. Therefore, applicants conclude the PGCs of Chang are not undifferentiated cells as claimed. Applicants' argument is not persuasive. The claims encompass cultures comprising avian cells having any ES cell phenotype. The PGCs of Chang meet the limitation because they obtained during development and contribute to the gonads – a phenotype of ES cells.

Claims 44, 47, 48 and 51-55 remain rejected and claims 56 and 57 are rejected under the judicially created doctrine of obviousness-type double patenting as being

unpatentable over claim 1 of U.S. Patent No. 5,656,479 or 5,830,510 in view of Chang (1995, Cell Biol. Internat'l., Vol. 19, page 143-9) for reasons of record.

Claim 1 of '479 and '510 are directed toward a sustained culture consisting essentially of undifferentiated avian cells expressing an embryonic cell phenotype. Claim 2 states the cells may be cultured on STO feeder cells in the presence of LIF. The cells were isolated from the area pellucida of Stage X embryos and cultured on mouse STO cells. The cells isolated in the disclosure of '479 and '510 inherently comprise stromal cells, which is equivalent to avian feeder cells as claimed in the instant invention. Thus, the claims of '479 and '510 in view of their respective disclosures meet all the limitations of claim 44 in the instant invention. In the alternative, '479 and '510 did not specifically teach a culture comprising PGCs and avian stromal cells isolated from the germinal ridge of an avian embryo at a stage later than stage 14.

However, at the time of filing, Chang taught culturing PGCs with avian stromal cells isolated from the genital ridge of a stage 27 embryo. Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to isolate avian cells having an ES cell phenotype as claimed in '479 and '510 wherein the avian cells are cultured on avian stromal cells isolated from Stage 27 embryos as taught by Chang. One of ordinary skill in the art at the time the invention was made would have been motivated to use stromal cells isolated from stage 27 avian embryos to increase the number of PGCs as taught by Chang (abstract).

Applicants' arguments are the same as those provided for the double patenting rejection above. Applicants' arguments are not persuasive and have been addressed above.

The rejection of claims 44, 47, 48 and 51-55 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-12 of U.S. Patent No. 6,156,569 in view of Chang (1995, Cell Biol. International., Vol. 19, page 143-9) has been withdrawn because '569 and the instant application have no common inventorship.

Conclusion

No claim is allowed.

Inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson who can normally be reached at the office on Monday, Tuesday, Thursday and Friday from 9:30 am to 6:00 pm at 571-272-0738.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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If attempts to reach the examiner are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on 571-272-0735.

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